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*JAMA.* 2007;298(2):194-206 (doi:10.1001/jama.298.2.194)

http://jama.ama-assn.org/cgi/content/full/298/2/194

# Efficacy and Safety of Incretin Therapy in Type 2 Diabetes

## Systematic Review and Meta-analysis

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**Context** Pharmacotherapies that augment the incretin pathway have recently become available, but their role in the management of type 2 diabetes is not well defined.

**Objective** To assess the efficacy and safety of incretin-based therapy in adults with type 2 diabetes based on randomized controlled trials published in peer-reviewed journals or as abstracts.

**Data Sources** We searched MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials (second quarter, 2007) for English-language randomized controlled trials involving an incretin mimetic (glucagonlike peptide 1 [GLP-1] analogue) or enhancer (dipeptidyl peptidase 4 [DPP4] inhibitor). We also searched prescribing information, relevant Web sites, reference lists and citation sections of recovered articles, and abstracts presented at recent conferences.

**Study Selection** Randomized controlled trials were selected if they were at least 12 weeks in duration, compared incretin therapy with placebo or other diabetes medication, and reported hemoglobin $A_{1c}$ data in nonpregnant adults with type 2 diabetes.

**Data Extraction** Two reviewers independently assessed trials for inclusion and extracted data. Differences were resolved by consensus. Meta-analyses were conducted for several efficacy and safety outcomes.

**Results** Of 355 potentially relevant articles identified, 51 were retrieved for detailed evaluation and 29 met the inclusion criteria. Incretins lowered hemoglobin $A_{1c}$ compared with placebo (weighted mean difference, –0.97% [95% confidence interval {CI}, –1.13% to –0.81%] for GLP-1 analogues and –0.74% [95% CI, –0.85% to –0.62%] for DPP4 inhibitors) and were noninferior to other hypoglycemic agents. Glucagonlike peptide 1 analogues resulted in weight loss (1.4 kg and 4.8 kg vs placebo and insulin, respectively) while DPP4 inhibitors were weight neutral. Glucagonlike peptide 1 analogues had more gastrointestinal side effects (risk ratio, 2.9 [95% CI, 2.0-4.2] for nausea and 3.2 [95% CI, 2.5-4.4] for vomiting). Dipeptidyl peptidase 4 inhibitors had an increased risk of infection (risk ratio, 1.2 [95% CI, 1.0-1.4] for nasopharyngitis and 1.5 [95% CI, 1.0-2.2] for urinary tract infection) and headache (risk ratio, 1.4 [95% CI, 1.1-1.7]). All but 3 trials had a 30-week or shorter duration; thus, long-term efficacy and safety could not be evaluated.

**Conclusions** Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant adults with type 2 diabetes, with modest efficacy and a favorable weight-change profile. Careful postmarketing surveillance for adverse effects, especially among the DPP4 inhibitors, and continued evaluation in longer-term studies and in clinical practice are required to determine the role of this new class among current pharmacotherapies for type 2 diabetes.

*JAMA. 2007;298(2):194-206* www.jama.com

FEWER THAN HALF OF US ADULTS with type 2 diabetes reach a hemoglobin $A_{1c}$ ($HbA_{1c}$) level of less than 7% despite several available therapies.[1] Ineffective implementation of existing pharmacotherapies is a significant factor contributing to suboptimal care.[2] However, efficacy of available therapies, even when used appropriately, diminishes as the disease progresses because of a steady, relentless decline in pancreatic beta cell function.[3] Furthermore, current therapies for type 2 diabetes are often limited by adverse effects such as weight gain, edema, or hypoglycemia, and most do not target postprandial hyperglycemia effectively. Therefore, therapies targeting the decline in pancreatic beta cell function without causing weight gain and with minimal adverse effects are desirable.

Recently, improved understanding of the incretin effect on the pathophysiology of type 2 diabetes has led to development of new hypoglycemic agents. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut.[4] The theory evolved from the observation that an oral glucose load was more effective at releasing insulin compared with the same amount of glucose given intravenously.[5] The actions of incre-

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tins depend on glucose concentration, and their function ceases when serum glucose level is less than 55 mg/dL (to convert to millimoles per liter, multiply by 0.0555).[4,6] The incretin effect is composed primarily of 2 peptides, glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide 1 (GLP-1). Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP4), resulting in a very short half-life (minutes). The incretin pathway appears to be attenuated in type 2 diabetes, making the pathway a target for development of new pharmacologic agents.[7,8]

In April 2005, the US Food and Drug Administration approved the first incretin mimetic, exenatide, a GLP-1 receptor analogue resistant to DPP4 degradation, as adjunctive therapy for patients with type 2 diabetes. Because GLP-1 analogues require injection, considerable effort has been devoted to creating an oral agent targeting the incretin pathway. Inhibition of DPP4 extends the half-life of native incretins, thereby prolonging their effects. In October 2006, the Food and Drug Administration approved the first oral incretin enhancer, sitagliptin, a selective DPP4 inhibitor, for use as monotherapy or in combination with metformin or thiazolidinedione. Additional incretin-based agents are in late-stage development.[8]

The present meta-analysis assesses the efficacy and safety of incretin-based therapy (GLP-1 analogues and DPP4 inhibitors) in nonpregnant adults with type 2 diabetes based on published and unpublished randomized controlled trials.

## METHODS

We followed the QUOROM (Quality of Reporting of Meta-analyses) guidelines for reporting our meta-analysis methods and results.[9]

### Data Sources and Searches

We conducted a search of MEDLINE (1966–May 20, 2007) and the Cochrane Central Register of Controlled Trials (second quarter, 2007) for English-language randomized controlled trials of incretin therapy (GLP-1 analogues and DPP4 inhibitors) in nonpregnant adults with type 2 diabetes. We used the following search terms: *diabetes*, *blood glucose*, *hyperglycemia*, *glucose*, *glycohemoglobin*, *hemoglobin* $A_{1c}$, *incretin*, *glucagon like peptide*, *enteroglucagon*, *GLP-1*, *GIP*, *exenatide*, *liraglutide*, *dipeptidyl peptidase*, *DPP*, *LAF237*, *MK-0431*, *sitagliptin*, *vildagliptin*, *saxagliptin*, *human*, and *clinical trial*. We searched for additional trials in the prescribing information documents of approved medications, at relevant Web sites (eg, http://www.clinicalstudyresults.org and http://www.clinicaltrials.gov), and in personal reference lists and citation sections of recovered articles. We also searched abstracts presented at the American Diabetes Association and the European Association Study of Diabetes conferences for 2005-2006. We included abstracts with data that had not been published in peer-reviewed journals because in our search of the relevant literature, we did not find any differences between trial results that were originally described in abstracts and those from the same trials that were subsequently published in peer-reviewed journals.

### Study Selection

Two reviewers (R.E.A. and A.G.P.) independently screened abstracts according to the inclusion criteria. An abstract was judged relevant if it reported original data from controlled trials in patients with type 2 diabetes with $HbA_{1c}$ outcomes for an incretin-based vs a non–incretin-based comparator group (placebo or hypoglycemic agent). We excluded studies of less than 12 weeks' duration because such studies would give an inadequate assessment of change in glycemic efficacy, as $HbA_{1c}$ reflects glycemia during the previous 3 months.[10] Full-text articles were retrieved and reviewed if a decision on inclusion could not be made solely based on the abstract. Any discrepancies were resolved by consensus between the 2 independent reviewers or in group conference via referencing the original article.

### Data Extraction and Quality Assessment

Participant baseline characteristics of the included studies were extracted and are described in TABLE 1. For glycemic efficacy, we extracted data on change from baseline in $HbA_{1c}$, fasting plasma glucose, and postprandial glycemia after a mixed-meal test and proportion of patients achieving $HbA_{1c}$ of less than 7%. When available, we also extracted data on change in body weight and lipid profile. To evaluate safety, we extracted data on hypoglycemia (severe or nonsevere) and all reported adverse events. We also extracted data on level of circulating antibodies to incretin analogue. For hypoglycemia, we combined and present data on the total number of patients per treatment group who reported at least 1 episode of hypoglycemia. Differences in baseline characteristics between groups, description of allocation concealment, intention-to-treat analysis, and dropout rate were used to evaluate study quality.

### Data Synthesis and Analysis

The primary measure for glycemic efficacy was the treatment group difference in $HbA_{1c}$ change from baseline. Treatment group difference in fasting plasma glucose and the proportion of participants reaching an $HbA_{1c}$ of less than 7% were secondary glycemic efficacy outcomes. For safety, we examined number of participants reporting hypoglycemia and other adverse effects. Because these 2 classes of medications are relatively new, to assess safety, we analyzed all reported adverse events.

For continuous variables ($HbA_{1c}$, fasting plasma glucose, weight), we calculated weighted mean differences and 95% confidence intervals (CIs) for change from baseline in incretin vs comparator (placebo or hypoglycemic agent) groups. For dichotomous variables (percentages achieving $HbA_{1c}$ <7% and percentages with hypoglycemia and adverse events), we calculated the risk ratios and 95% CIs for incretin vs comparator groups. If data from more than 2 trials were available,

**Table 1.** Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review

| Source[a] | Study Duration, wk | No. of Participants[b] | Mean Age, y/ Women, %/ White, % | Duration of Diabetes, y | Baseline $HbA_{1c}$ Level, % | Incretin-Based Therapy[c] | Control[c] | Study Quality[d]: Allocation Concealment Described? | Study Quality[d]: Data Analysis | Study Quality[d]: Dropout Rate, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Exenatide | | | | | | | | | | |
| Buse et al,[11] 2004 | 30 | 377 | 55/40/63 | 6 | 8.6 | Sulfonylurea + exenatide, 10 μg<br>Sulfonylurea + exenatide, 5 μg[e] | Sulfonylurea + placebo injection (subcutaneous twice daily) | No | ITT | 31 |
| DeFronzo et al,[12] 2005 | 30 | 336 | 53/43/76 | 6 | 8.2 | Metformin + exenatide, 10 μg<br>Metformin + exenatide, 5 μg[e] | Metformin + placebo injection (subcutaneous twice daily) | No | ITT | 19 |
| Kendall et al,[13] 2005 | 30 | 734 | 55/42/68 | 9 | 8.5 | Sulfonylurea/ metformin + exenatide, 5 μg[e]<br>Sulfonylurea/ metformin + exenatide, 10 μg | Sulfonylurea/ metformin + placebo injection (subcutaneous twice daily) | No | ITT | 19 |
| Heine et al,[14] 2005[f] | 26 | 551 | 59/44/80 | 10 | 8.2 | Sulfonylurea/ metformin + exenatide, 10 μg | Sulfonylurea/ metformin + insulin glargine | Yes | APT | 15 |
| Nauck et al,[15] 2007[f] | 52 | 505 | 59/49/NR | 10 | 8.6 | Sulfonylurea/ metformin + exenatide, 10 μg | Sulfonylurea/ metformin + biphasic aspart insulin | Yes | APT | 16 |
| Zinman et al,[16] 2007 | 16 | 233 | 56/45/84 | 8 | 7.9 | Thiazolidinedione (pioglitazone or rosiglitazone)/ metformin + exenatide, 10 μg | Thiazolidinedione (pioglitazone or rosiglitazone)/ metformin + placebo injection (subcutaneous twice daily) | Yes | ITT | 22 |
| Kim et al,[17] 2007 | 15 | 45 | 53/40/60 | 5 | 8.5 | Metformin/diet + exenatide (subcutaneous once/wk), 2.0 mg<br>Metformin/diet + exenatide (subcutaneous once/wk), 0.8 mg[e] | Metformin/diet + placebo injection (subcutaneous once/wk) | No | ITT | 4 |
| Liraglutide | | | | | | | | | | |
| Madsbad et al,[18] 2004 | 12 | 193 | 58/33/100 | 4 | 7.4 | Liraglutide, 0.75 mg<br>Liraglutide, 0.6 mg[e] | Placebo injection (subcutaneous twice daily) | No | ITT | 13 |
| Feinglos et al,[19] 2005 | 12 | 210 | 54/60/78 | 5 | 7.0 | Liraglutide, 0.75 mg<br>Liraglutide, 0.6 mg[e] | Metformin | No | Completers | 15 |
| Sitagliptin | | | | | | | | | | |
| Scott et al,[20] 2007 | 12 | 743 | 55/45/65 | 5 | 7.9 | Sitagliptin, 50 mg twice daily<br>Sitagliptin, 5 mg twice daily[e]<br>Sitagliptin, 12.5 mg twice daily[e]<br>Sitagliptin, 25 mg twice daily[e] | Placebo | No | APT | 12 |
| Raz et al,[21] 2006 | 18 | 521 | 55/46/68 | 5 | 8.1 | Sitagliptin, 100 mg once daily<br>Sitagliptin, 200 mg once daily[e] | Placebo | No | APT | 11 |
| Ascher et al,[22] 2006 | 24 | 741 | 54/46/51 | 4 | 8.0 | Sitagliptin, 100 mg once daily<br>Sitagliptin, 200 mg once daily[e] | Placebo | No | APT | 14 |
| Charbonnel et al,[23] 2006 | 24 | 701 | 55/43/64 | 6 | 8.0 | Metformin + sitagliptin, 100 mg once daily | Metformin + placebo | No | APT | 13 |

*(continued)*

we combined data from trials within a class (GLP-1 analogues or DPP4 inhibitors) and explored heterogeneity between comparable trials with prespecified subgroup analyses by type of comparator group (placebo vs hypoglycemic agent), duration of intervention (12 vs >12 weeks), and available formulation within each class. For dose-dependent outcomes, such as glycemic efficacy ($HbA_{1c}$, percentage achieving $HbA_{1c}$ >7%), weight change, and hypoglycemia, only data from the approved maximum dose entered the meta-analyses (10 µg twice daily for exenatide and 100 mg/d for sitagliptin). For nonapproved medications, the highest dose was used (0.75 mg/d for liraglutide, 2.0 mg once weekly for exenatide given subcutaneously, and 100 mg/d for vildagliptin). For adverse-event outcomes, we included data from all available doses to increase the statistical power to detect differences between treatment groups of uncommon events.

For postprandial glycemia, lipid profile, and antibody development, we did not perform meta-analyses because of the diverse methods used to assess out-

**Table 1.** Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review (cont)

| Source[a] | Study Duration, wk | No. of Participants[b] | Mean Age, y/ Women, %/ White, % | Duration of Diabetes, y | Baseline $HbA_{1c}$ Level, % | Incretin-Based Therapy[c] | Control[c] | Study Quality[d]: Allocation Concealment Described? | Study Quality[d]: Data Analysis | Study Quality[d]: Dropout Rate, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Sitagliptin | | | | | | | | | | |
| Rosenstock et al,[24] 2006 | 24 | 353 | 56/44/73 | 6 | 8.1 | Pioglitazone + sitagliptin, 100 mg once daily | Pioglitazone + placebo | No | APT | 13 |
| Nauck et al,[25] 2007[f] | 52 | 1172 | 57/41/74 | 6 | 7.7 | Metformin + sitagliptin, 100 mg once daily | Metformin + glipizide | No | APT | 32 |
| Nonaka et al,[26] 2006[g] | 12 | 151 | 55/49/NR | 4 | 7.6 | Sitagliptin, 100 mg once daily | Placebo | No | APT | NR |
| Hanefeld et al,[27] 2005[g] | 12 | 555 | 56/48/NR | 4 | 7.7 | Sitagliptin, 100 mg once daily<br>Sitagliptin 50 mg twice daily[e]<br>Sitagliptin, 25 mg once daily[e]<br>Sitagliptin, 50 mg once daily[e] | Placebo | No | APT | NR |
| Vildagliptin | | | | | | | | | | |
| Ahren et al,[28] 2004 | 12 | 107 | 57/32/99 | 6 | 7.8 | Metformin + vildagliptin, 50 mg once daily | Metformin + placebo | No | ITT | 10 |
| Ristic et al,[29] 2005 | 12 | 279 | 56/46/80 | 3 | 7.7 | Vildagliptin, 100 mg once daily<br>Vildagliptin, 25 mg twice daily[e]<br>Vildagliptin, 25 mg once daily[e]<br>Vildagliptin, 50 mg once daily[e] | Placebo | No | ITT | NR |
| Pratley et al,[30] 2006 | 12 | 100 | 56/57/47 | 4 | 8.0 | Vildagliptin, 25 mg twice daily | Placebo | No | ITT | 9 |
| Pi-Sunyer et al,[31] 2007 | 24 | 354 | 51/45/54 | 2 | 8.4 | Vildagliptin, 100 mg once daily<br>Vildagliptin, 50 mg once daily[e]<br>Vildagliptin, 50 mg twice daily[e] | Placebo | No | APT | 23 |
| Dejager et al,[32] 2007 | 24 | 632 | 54/53/73 | 2 | 8.4 | Vildagliptin, 100 mg once daily<br>Vildagliptin, 50 mg once daily[e]<br>Vildagliptin, 50 mg twice daily[e] | Placebo | No | ITT | 19 |
| Garber et al,[33] 2007 | 24 | 463 | 54/50/80 | 5 | 8.7 | Pioglitazone + vildagliptin, 50 mg twice daily<br>Pioglitazone + vildagliptin, 50 mg once daily[e] | Pioglitazone + placebo | No | APT | 19 |

(continued)

comes and/or because of insufficiently reported data. For all meta-analyses, we used a random-effects model that weighs studies by the inverse of the within-study and between-studies variances.[40] Most studies reported differences in the mean changes and the corresponding 95% CIs (or standard errors) between comparison groups. For studies that reported only the mean changes and the corresponding standard errors of the mean change, we calculated the differences and the standard errors of the differences between comparison groups using these data. We used the $I^2$ statistic to quantify the degree of heterogeneity among trials in each meta-analysis.[41] Event rates of single groups across studies (eg, hypoglycemia, adverse events) were calculated using a random-effects model to combine the logits of the event rates then transforming back to the rates (percentages).

## RESULTS

### Search Results and Study Characteristics

Search results are summarized in FIGURE 1. The characteristics of the 29 included trials (articles and abstracts) are summarized in Table 1. Only 3 of the 29 studies had durations of longer than 30 weeks.

There were 8 published trials (n=3139; age range, 19-78 years) in which a GLP-1 analogue was added to existing inadequate therapy (lifestyle or oral hypoglycemic therapy) and compared with a double-blind injectable placebo,[11-13,16,18] metformin,[19] or open-label subcutaneous insulin (glargine or biphasic aspart).[14,15] There was also 1 small study (n=45) with a long-acting formulation of a GLP-1 analogue.[17]

There were 13 published double-blind trials (n=4780; age range, 18-80 years) in which a placebo was compared with a DPP4 inhibitor given as monotherapy[20-22,29-32] or as add-on therapy to oral hypoglycemic

**Table 1.** Characteristics of Randomized Controlled Trials of Glucagonlike Peptide 1 Analogues and Dipeptidyl Peptidase 4 Inhibitors Included in the Systematic Review (cont)

| | | | | | | | | Study Quality[d] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Source[a] | Study Duration, wk | No. of Participants[b] | Mean Age, y/ Women, %/ White, % | Duration of Diabetes, y | Baseline $HbA_{1c}$ Level, % | Incretin-Based Therapy[c] | Control[c] | Allocation Concealment Described? | Data Analysis | Dropout Rate, % |
| Vildagliptin | | | | | | | | | | |
| Rosenstock et al,[34] 2007[f] | 24 | 786 | 54/42/80 | 2 | 8.7 | Vildagliptin, 50 mg twice daily | Rosiglitazone, 8 mg once daily | No | APT | 14 |
| Bosi et al,[35] 2007 | 24 | 544 | 54/43/74 | 6 | 8.4 | Metformin + vildagliptin, 50 mg twice daily<br>Metformin + vildagliptin, 50 mg once daily[e] | Metformin + placebo | No | APT | 15 |
| Rosenstock et al,[36] 2007[h] | 24 | 315 | 52/36/42 | 2 | 8.7 | Vildagliptin, 100 mg once daily | Pioglitazone, 30 mg once daily | No | APT | 15 |
| Fonseca et al,[37] 2007 | 24 | 296 | 59/49/71 | 15 | 8.4 | Unspecified insulin therapy + vildagliptin, 50 mg twice daily | Unspecified insulin therapy + placebo | No | APT | 19 |
| Schweizer et al,[38] 2007[f] | 52 | 780 | 53/46/68 | 1 | 8.7 | Vildagliptin, 50 mg twice daily | Metformin, 1000 mg twice daily | No | APT | 27 |
| Mimori et al,[39] 2006[g] | 12 | 219 | 59/NR/NR | NR | 7.4 | Vildagliptin, 50 mg twice daily<br>Vildagliptin, 10 mg twice daily[e]<br>Vildagliptin, 25 mg twice daily[e] | Placebo | No | NR | NR |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$; NR, not reported.

[a] All studies were multinational except Buse et al,[11] Defronzo et al,[12] and Kendall et al.[13] Women who were pregnant or breastfeeding or those with reproductive potential who were not using contraceptives were excluded.

[b] The total number of participants randomized to all groups is different from the number of participants used in meta-analyses of glycemic efficacy, weight change, and hypoglycemia outcomes because most articles reported a modified ITT analysis ("all patients treated") that did not include all randomized participants and because only the highest available dose entered these meta-analyses.

[c] Plus sign indicates that the study medication (active or control) was added to existing therapy. Neither glucagonlike peptide 1 analogues nor dipeptidyl peptidase 4 inhibitors were titrated according to study-specific glucose goals. Exenatide or placebo injection was given subcutaneously twice daily approximately 15 minutes before a meal, titrated to the higher dose after an acclimation period, unless otherwise specified. Liraglutide or placebo injection was given subcutaneously once daily approximately 15 minutes before breakfast. When not specified, sulfonylurea drug was glyburide, glipizide, or glibenclamide.

[d] Few studies reported whether they tested for balanced baseline characteristics between comparison groups. No differences were noted in the most important characteristics (age, weight, $HbA_{1c}$, and duration of diabetes) except in the studies by Buse et al,[11] Defronzo et al,[12] Madsbad et al,[16] and Dejager et al,[32] in which small differences were noted between groups at baseline. Intention-to-treat (ITT) analyses were defined as those in which all randomized patients who received at least 1 dose of study treatment were included in the analysis; "all patients treated" (APT) analyses were defined as those in which all randomized patients who received at least 1 dose of study treatment and who had both a baseline and at least 1 postbaseline measurement were included; "completers" analyses were defined as those in which participants with complete data at the last follow-up visit were included.

[e] Study groups with lower doses or nonapproved doses were used in meta-analyses for adverse events only.

[f] Noninferiority trials.

[g] Data were available from abstracts only.

[h] Study had 2 additional groups (vildagliptin, 100 mg daily, combined with pioglitazone, 30 mg daily; and vildagliptin, 50 mg daily, combined with pioglitazone, 15 mg daily), which were not used in the meta-analyses.

agents[23,24,28,33,35] or insulin.[37] Four published trials (n=3053) directly compared a DPP4 inhibitor with a hypoglycemic agent, including glipizide titrated to glycemic goals,[25] metformin,[38] or a thiazolidenedione.[34,36] There were 3 abstracts concerning a DPP4 inhibitor (n=925), with data contributing only to certain meta-analyses.[26,27,39]

### Methodological Quality

All studies included a control group (placebo or hypoglycemic agent) in a double-blind design, except the studies involving insulin, which were open-label.[14,15] Eligibility criteria were clearly reported in all trials. Concealment allocation was clearly described in only 3 studies.[14-16] Few studies reported whether they tested for balanced baseline characteristics (eg, age, weight, $HbA_{1c}$, and duration of diabetes) between comparison groups. We noted small baseline differences in only 3 studies.[11,12,18] Participant withdrawal was approximately 19% in the GLP-1 analogue studies (19% with exenatide and 12% with liraglutide) and 18% in the DPP4 inhibitor studies (20% with sitagliptin and 16% with vildagliptin). Withdrawals were primarily due to loss of glycemic efficacy in the placebo groups and gastrointestinal adverse effects in the exenatide treatment groups. All studies were funded by pharmaceutical companies; the role of the sponsor was clearly disclosed in only 2 studies.[14,16]

### Incretin Mimetics (GLP-1 Analogues)

Glycemic Outcomes. *Hemoglobin $A_{1C}$.* Combining data from studies comparing GLP-1 analogues with placebo injection showed a statistically significant difference in $HbA_{1c}$ decline from baseline favoring incretin therapy (weighted mean difference, −0.97%; 95% CI, −1.13% to −0.81%) (FIGURE 2).[11-13,16-18] There was no difference in $HbA_{1c}$ in open-label noninferiority studies between exenatide and insulin glargine or biphasic aspart.[14,15] Liraglutide showed similar $HbA_{1c}$ efficacy compared with open-label glimepiride titrated to glycemic goals[18] or double-blind, maximum-dose metformin.[19]

Patients receiving exenatide were more likely to achieve an $HbA_{1c}$ of less than 7% compared with patients receiving placebo (45% vs 10%, respectively; risk ratio, 4.2; 95% CI, 3.2-5.5),[11-13,16] but there was no difference between exenatide and insulin in noninferiority trials (39% vs 35%, respectively; risk ratio, 1.1; 95% CI, 0.8-1.5) (TABLE 2).[14,15]

*Fasting and Postprandial Glycemia.* Fasting plasma glucose was reduced with a GLP-1 analogue compared with placebo injection (weighted mean difference, −27 mg/dL; 95% CI, −33 to −21 mg/dL) (Table 2).[11-13,16-18] In the open-label studies comparing exenatide vs insulin glargine or biphasic aspart, postprandial glycemia was reduced more with exenatide,[14,15] while there was no difference in fasting plasma glucose (weighted mean difference, 13 mg/dL; 95% CI, −16 to 41 mg/dL). In mixed-meal testing,

**Figure 1.** Study Design

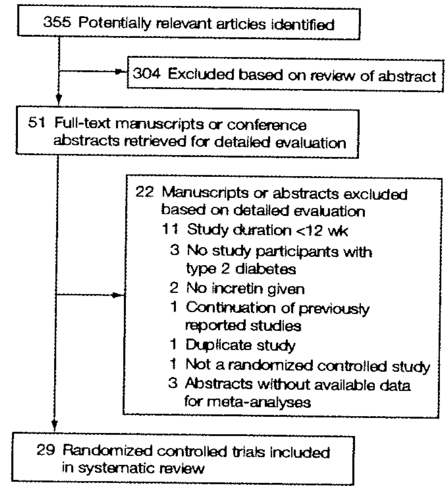
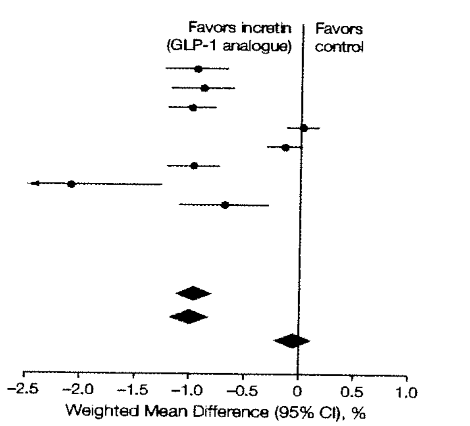



**Figure 2.** Weighted Mean Difference in Change in Hemoglobin $A_{1c}$ Percentage Value for GLP-1 Analogues vs Control in Adults With Type 2 Diabetes

| Source | Study Duration, wk | No.of Participants | Weighted Mean Difference (95% CI) for Change in Hemoglobin $A_{1C}$, % | |
|---|---|---|---|---|
| Buse et al,[11] 2004 | 30 | 252 | −0.96 (−1.24 to −0.68) | |
| DeFronzo et al,[12] 2005 | 30 | 226 | −0.90 (−1.18 to −0.62) | |
| Kendall et al,[13] 2005 | 30 | 488 | −1.00 (−1.21 to −0.79) | |
| Heine et al,[14] 2005 | 26 | 535 | 0.02 (−0.12 to 0.16) | |
| Nauck et al,[15] 2007 | 52 | 501 | −0.15 (−0.32 to 0.01) | |
| Zinman et al,[16] 2007 | 16 | 233 | −0.98 (−1.21 to −0.74) | |
| Kim et al,[17] 2006 | 15 | 29 | −2.10 (−2.93 to −1.27) | |
| Madsad et al,[18] 2004 | 12 | 57 | −0.75 (−1.10 to −0.40) | |
| **Comparisons** | **No. of Studies** | | | **$I^2$, %** |
| GLP-1 vs placebo[11-13,16-18] | 6 | 1285 | −0.97 (−1.13 to −0.81) | 44 |
| Exenatide vs placebo[11-13,16] | 5 | 1228 | −1.01 (−1.18 to −0.84) | 45 |
| Exenatide vs insulin[14,15] | 2 | 1036 | −0.06 (−0.22 to 0.10) | 59 |




CI indicates confidence interval; GLP-1, glucagonlike peptide 1. The $I^2$ statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

exenatide produced a dose-dependent decrease in postprandial glucose excursions up to 87% at the highest dose compared with baseline.[12-14]

**Nonglycemic Outcomes.** *Weight.* In trials that reported data on changes in weight,[11-18] there was a statistically significant weight loss observed with GLP-1 analogues vs comparator groups (weighted mean difference, −2.37 kg; 95% CI −3.95, −0.78). The weight loss was more pronounced when ex-

**Table 2.** Summary of Meta-analyses of Outcomes in Patients With Type 2 Diabetes Treated With Incretin-Based Therapy vs Non–Incretin-Based Therapy (Controls)

| Outcome | No. of Studies Contributing Data | Risk Ratio (95% CI), Incretin vs Control | Weighted Mean Difference (95% CI) in Change From Baseline, Incretin vs Control | $I^2$ Heterogeneity, % | Incretin-Based Therapy: Mean % (95% CI) Achieving Outcome | Incretin-Based Therapy: No. of Participants With Data Analyzed | Control: Mean % (95% CI) Achieving Outcome | Control: No. of Participants With Data Analyzed |
|---|---|---|---|---|---|---|---|---|
| **GLP-1 Analogues** | | | | | | | | |
| Achieved $HbA_{1c}$ <7% | | | | | | | | |
| Exenatide vs placebo injection[11-13,16,17] | 5 | 4.19 (3.17-5.53) | | | 45 (32-60) | 561 | 10 (7-14) | 562 |
| Exenatide vs insulin[14,15] | 2 | 1.10 (0.81-1.50) | | | 39 (26-53) | 502 | 35 (16-60) | 497 |
| Fasting plasma glucose level, mg/dL | | | | | | | | |
| All GLP-1 analogues vs placebo injection[11-13,16-19] | 7 | | −27 (−33 to −21) | 11 | | | | |
| Exenatide vs placebo injection[11-13,16,17] | 5 | | −27 (−34 to −20) | 34 | | | | |
| Exenatide vs insulin[14,15] | 2 | | 13 (−16 to 41) | 96 | | | | |
| Weight, kg | | | | | | | | |
| All GLP-1 analogues vs control[11-18a] | 8 | | −2.37 (−3.95 to −0.78) | 98 | | | | |
| Exenatide vs placebo injection[11-13,16,17] | 5 | | −1.44 (−2.13 to −0.75) | 92 | | | | |
| Exenatide vs insulin[14,15] | 2 | | −4.76 (−6.03 to −3.49) | 70 | | | | |
| **DPP4 Inhibitors** | | | | | | | | |
| Achieved $HbA_{1c}$ <7% | | | | | | | | |
| All DPP4 inhibitors vs placebo[15,21-24,26,28,29,31,33] | 9 | 2.47 (2.14-2.84) | | | 43 (39-47) | 1442 | 17 (15-20) | 1146 |
| Sitagliptin vs placebo[15,21-24,26] | 5 | 2.43 (2.03-2.92) | | | 44 (39-51) | 1113 | 18 (16-21) | 821 |
| Vildagliptin vs placebo[28,29,31,33] | 4 | 2.40 (1.78-3.24) | | | 38 (31-45) | 317 | 15 (11-20) | 325 |
| All DPP4 inhibitors vs hypoglycemic agents[25,36,38b] | 3 | 0.93 (0.77-1.11) | | | 43 (32-55) | 1237 | 47 (42-52) | 965 |
| Fasting plasma glucose level, mg/dL | | | | | | | | |
| All DPP4 inhibitors vs placebo[20-24,26-31,33,35,37,39] | 15 | | −18 (−22 to −14) | 63 | | | | |
| Sitagliptin vs placebo[20-24,26,27] | 7 | | −22 (−26 to −18) | 50 | | | | |
| Vildagliptin vs placebo[28-31,33,35,37,39] | 8 | | −12 (−16 to −7) | 3 | | | | |
| All DPP4 inhibitors vs hypoglycemic agents[25,34,36,38b] | 4 | | 11 (−1 to 123) | 91 | | | | |
| Weight, kg | | | | | | | | |
| All DPP4 inhibitors vs placebo[20-22,24,26,28-33,35,37] | 13 | | 0.48 (0.30 to 0.66) | 0 | | | | |
| Sitagliptin vs placebo[20-22,24,26] | 5 | | 0.52 (0.28 to 0.76) | 4 | | | | |
| Vildagliptin vs placebo[28-33,35,37] | 8 | | 0.42 (0.12 to 0.72) | 0 | | | | |

Abbreviations: CI, confidence interval; DPP4, dipeptidyl peptidase 4; GLP-1, glucagonlike peptide 1; $HbA_{1c}$, hemoglobin $A_{1c}$.
SI conversion: To convert glucose to mmol/L, multiply by 0.0555.
[a] Control is placebo injection or insulin.
[b] Hypoglycemic agents were glipizide, rosiglitazone, pioglitazone, or metformin.

enatide was compared with insulin (Table 2).[14,15] Weight loss with exenatide was progressive, dose-dependent, and without apparent plateau by week 30.[11-16] Several studies noted a nonsignificant trend toward greater weight reduction in patients who experienced at least 1 episode of nausea while receiving exenatide.[11,14,15] However, participants who did not report nausea also lost weight.[11-16] Weight loss was less pronounced with liraglutide.[18,19]

*Lipids.* In the 3 trials that reported data,[11,15,16] there were no changes in lipid profile with the exception of a small improvement in high-density lipoprotein cholesterol favoring biphasic aspart insulin over exenatide[15] and a small decrease in low-density lipoprotein cholesterol favoring exenatide over placebo injection.[11]

Adverse Events. *Hypoglycemia.* Severe hypoglycemia (requiring assistance) was rare with GLP-1 analogues, reported in only 5 of 2781 patients treated with exenatide and only in patients who also received sulfonylurea.[13,14] When data were combined, mild to moderate hypoglycemia was more commonly reported in exenatide vs placebo injection (16% vs 7%, respectively; risk ratio, 2.3; 95% CI, 1.1-4.9), especially when coadministered with a sulfonylurea.[11,13] Hypoglycemia peaked during initiation of therapy with exenatide then decreased over time.[11,13,14,18] The risk of hypoglycemia was similar between exenatide vs insulin (≈2% in both groups; risk ratio, 1.0; 95% CI, 0.5-2.3).[14,15] Hypoglycemia was less common with liraglutide compared with glimepiride (6% vs 35%, respectively) in the single study with such data.[18]

*Other Adverse Events.* Dose-dependent nausea and vomiting were the most frequently reported adverse events with exenatide vs a comparator (risk ratio, 2.9 [95% CI, 2.0-4.2] for nausea and 3.3 [95% CI, 2.5-4.4] for vomiting), occurring in as many as 57% (nausea) and 17% (vomiting) of patients treated with exenatide (Table 2). Nausea was generally mild to moderate, peaked during the initial 8 weeks and declined thereafter, and was attenuated by dose titration.[11-14] Diarrhea was also more likely to occur with exenatide vs a comparator (risk ratio, 2.2; 95% CI, 1.7-2.9). Gastrointestinal adverse effects led to higher withdrawal compared with placebo, with approximately 4% of participants treated with exenatide withdrawing because of gastrointestinal adverse effects.[11-15] Liraglutide was not associated with nausea or vomiting.[18,19]

*Antibodies.* There was a high incidence of development of antibodies to exenatide (up to 67% of patients), which was not associated with any effect on outcomes or adverse events.[11-17] Development of antibodies was not reported in the liraglutide studies.[18,19]

### Incretin Enhancers (DPP4 Inhibitors)

Glycemic Outcomes. *Hemoglobin $A_{1C}$.* Dipeptidyl peptidase 4 inhibitors lowered $HbA_{1c}$ compared with placebo[20-24,26-33,35,37,39] (weighted mean difference, −0.74%; 95% CI, −0.85% to −0.62%) (FIGURE 3) with similar efficacy as monotherapy or add-on therapy. The 2 available DPP4 inhibitors have not been compared directly, but both appeared to lower $HbA_{1c}$ similarly compared with placebo (−0.74% vs −0.73% for sitagliptin and vildagliptin respectively; Figure 3). Combining available data from 4 trials, DPP4 inhibitors were slightly less effective compared with other hypoglycemic agents (weighted mean difference, 0.21%; 95% CI, 0.02%-0.39%) (Figure 3). In the individual trials, noninferiority was established when sitagliptin was compared with glipizide[25] and vildagliptin with thiazolidinediones[34,36] but noninferiority was not shown when vildagliptin was compared with metformin.[38]

Patients receiving DPP4 inhibitors were more likely to achieve an $HbA_{1c}$ of less than 7% compared with placebo (43% vs 17%, respectively; risk ratio, 2.5%; 95% CI, 2.1-2.8) without any differences between sitagliptin and vildagliptin (Table 2).

*Fasting and Postprandial Glycemia.* Fasting plasma glucose was reduced with DPP4 inhibitors compared with placebo (weighted mean difference, −18 mg/dL; 95% CI, −22 to −14 mg/dL) (Table 2), with sitagliptin appearing to be more effective than vildagliptin.[20-24,26-33,35,39] In participants who underwent a mixed-meal tolerance test, statistically significant postprandial decreases in glycemia with sitagliptin measured at 2 hours postprandially[20-23,26] and with vildagliptin measured at 2 hours[33,35,39] or 4 hours postprandially[28-30] were observed, especially at higher doses.

Nonglycemic Outcomes. *Weight.* Thirteen trials reported data on weight.[20-22,24,26,28-33,35,37] There was a small increase in weight with DPP4 inhibitors compared with placebo (weighted mean difference, 0.5 kg; 95% CI, 0.3-0.7 kg). In noninferiority trials, sitagliptin had favorable weight profile compared with glipizide[25] (−2.5 kg vs 1.0 kg, respectively) and vildagliptin had a favorable weight profile compared with thiazolidinediones (weighted mean difference, −1.7, kg; 95% CI, −2.2 kg to −1.2 kg])[34,36] but not compared with metformin (2.2-kg weight loss favoring metformin).[38]

*Lipids.* There were no consistent changes in lipid profile with either sitagliptin[20,22-25] or vildagliptin[28-35,37,38] compared with placebo, but there were some improvements in triglycerides[20,23,24,35] and low- and high-density lipoprotein cholesterol.[20,23,25,37] Relative to rosiglitazone, vildagliptin decreased total cholesterol, triglycerides, and low-density lipoprotein cholesterol but produced a smaller increase in high-density lipoprotein cholesterol.[34] Relative to pioglitazone, vildagliptin decreased total and low-density lipoprotein cholesterol.[36] Vildagliptin also had favorable change in triglycerides compared with metformin.[35]

Adverse Events. *Hypoglycemia.* Severe hypoglycemia (requiring assistance) was reported in only 2 patients receiving DPP4 inhibitors. There was no difference in reported mild to moderate hypoglycemia between DPP4 inhibitors and a comparator group (1.6%

vs 1.4%, respectively; risk ratio, 1.0; 95% CI, 0.5-1.9) (TABLE 3).

*Other Adverse Events.* Studies with DPP4 inhibitors reported no risk of gastrointestinal adverse effects (nausea, vomiting, diarrhea, and abdominal pain) compared with placebo (Table 3). Dipeptidyl peptidase 4 inhibitors were overall very well tolerated, with low absolute rates of adverse effects. After combining studies with available data, there was an increased risk of nasopharyngitis (6.4% for DPP4 inhibitor vs 6.1% for comparator; risk ratio, 1.2; 95% CI, 1.0-1.4), which was more evident with sitagliptin, and an increased risk of urinary tract infection (3.2% for DPP4 inhibitor vs 2.4% for comparator; risk ratio, 1.5; 95% CI, 1.0-2.2), which was reported with both DPP4 inhibitors. Headache was also reported more commonly with DPP4 inhibitors (5.1% for DPP4 inhibitor vs 3.9% for comparator; risk ratio, 1.4; 95% CI, 1.1-1.7), especially with vildagliptin.

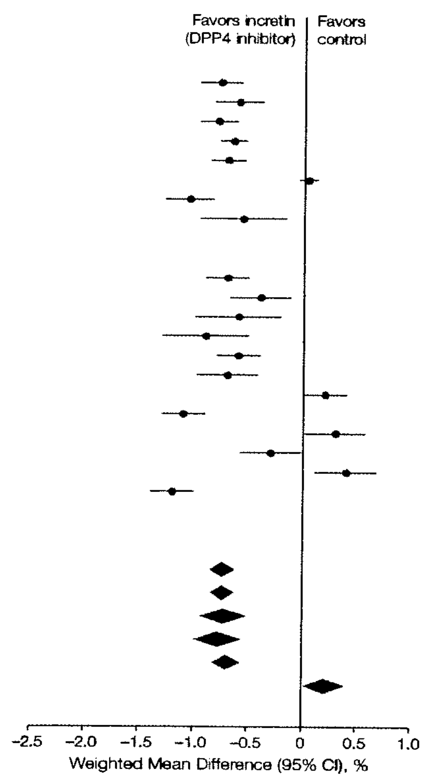
## COMMENT

The introduction of a new class of medications is generally a welcome addition to the existing armamentarium against type 2 diabetes with its associated severe morbidity and mortality. However, new medications are prized and are often quickly embraced over older, well-established, and effective medications despite limited ability to judge the merits of new medications in relation to long-term effectiveness and safety soon after approval for clinical use.[2] Aggressive marketing campaigns to physicians and direct-to-consumer advertisement also contribute to early widespread use of new medications. Our analysis of randomized controlled trials showed that incretin-based therapy with GLP-1 analogues or DPP4 inhibitors in adults with type 2 diabetes is moderately effective in improving glycemia, with greater reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP4 inhibitors) effects on weight. Glucagonlike peptide 1 analogues were associated with gastrointestinal adverse effects, while DPP4 inhibitors had a slightly increased risk of infection (nasopharyngitis and urinary tract infection) and headache.

The moderate lowering in $HbA_{1c}$ compared with placebo with incretin

**Figure 3.** Weighted Mean Difference in Change in Hemoglobin $A_{1c}$ Percentage Value for DPP4 Inhibitors vs Control in Adults With Type 2 Diabetes

| Source | Study Duration, wk | No. of Participants | Weighted Mean Difference (95% CI) for Change in Hemoglobin $A_{1c}$, % | $I^2$, % |
|---|---|---|---|---|
| **Sitagliptin** | | | | |
| Scott et al,[20] 2007 | 12 | 249 | −0.77 (−0.96 to −0.58) | |
| Raz et al,[21] 2006 | 18 | 296 | −0.60 (−0.82 to −0.38) | |
| Aschner et al,[22] 2006 | 24 | 473 | −0.79 (−0.96 to −0.62) | |
| Charbonnel et al,[23] 2006 | 24 | 677 | −0.65 (−0.77 to −0.53) | |
| Rosenstock et al,[24] 2006 | 24 | 337 | −0.70 (−0.86 to −0.54) | |
| Nauck et al,[25] 2007 | 52 | 1135 | 0.04 (−0.05 to 0.13) | |
| Nonaka et al,[26] 2006 | 12 | 151 | −1.05 (−1.27 to −0.83) | |
| Hanefeld et al,[27] 2005 | 12 | 221 | −0.56 (−0.95 to −0.17) | |
| **Vildagliptin** | | | | |
| Ahren et al,[28] 2004 | 12 | 107 | −0.70 (−0.90 to −0.50) | |
| Ristic et al,[29] 2005 | 12 | 121 | −0.40 (−0.67 to −0.13) | |
| Pratley et al,[30] 2006 | 12 | 98 | −0.60 (−0.99 to −0.21) | |
| Pi-Sunyer et al,[31] 2007 | 24 | 177 | −0.90 (−1.30 to −0.50) | |
| Dejager et al,[32] 2007 | 24 | 299 | −0.60 (−0.80 to −0.40) | |
| Garber et al,[33] 2007 | 24 | 274 | −0.70 (−0.98 to −0.42) | |
| Rosenstock et al,[34] 2007 | 24 | 697 | 0.20 (−0.01 to 0.39) | |
| Bosi et al,[35] 2007 | 24 | 273 | −1.10 (−1.30 to −0.90) | |
| Rosenstock et al,[36] 2007 | 24 | 307 | 0.30 (0.02 to 0.58) | |
| Fonseca et al,[37] 2007 | 24 | 289 | −0.30 (−0.58 to −0.02) | |
| Schweizer et al,[38] 2007 | 52 | 760 | 0.40 (0.12 to 0.68) | |
| Mimori et al,[39] 2006 | 12 | 148 | −1.20 (−1.39 to −1.01) | |
| **Comparisons** | **No. of Studies** | | | |
| DPP4 vs placebo[20-24,26-33,35,37,39] | 16 | 4190 | −0.74 (−0.85 to −0.62) | 77 |
| Sitagliptin vs placebo[20-24,26,27] | 7 | 2404 | −0.74 (−0.84 to −0.63) | 54 |
| Vildagliptin vs placebo[28-33,35,37,39] | 9 | 1786 | −0.73 (−0.94 to −0.52) | 85 |
| Duration 12 wk vs placebo[20,26-30,39] | 7 | 1095 | −0.78 (−1.00 to −0.56) | 82 |
| Duration 12-24 wk vs placebo[21-24,31-33,35,37] | 9 | 3095 | −0.70 (−0.83 to −0.58) | 72 |
| DPP4 vs hypoglycemic agent[25,34,36,38] | 4 | 2899 | 0.21 (0.02 to 0.39) | 66 |




The $I^2$ statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. CI indicates confidence interval; DPP4, dipeptidyl peptidase 4.

**Table 3.** Summary of Adverse Events in Patients With Type 2 Diabetes Treated With Incretin-Based vs Non–Incretin-Based Therapy

| | | | Incretin-Based Therapy | | Control | |
|---|---|---|---|---|---|---|
| Adverse Event | No. of Studies Contributing Data | Risk Ratio (95% CI), Incretin vs Control | Mean % (95% CI) Achieving Outcome | No. of Participants With Data Analyzed | Mean % (95% CI) Achieving Outcome | No. of Participants With Data Analyzed |
| **GLP-1 Analogues** | | | | | | |
| Hypoglycemia | | | | | | |
| Exenatide vs placebo injection[11-13,16,17] | 5 | 2.30 (1.08-4.88) | 16.0 (8.1-29.1) | 619 | 7.0 (4.0-12.0) | 609 |
| Exenatide vs insulin[14,15] | 2 | 1.02 (0.46-2.26) | 2.3 (1.3-4.1) | 520 | 2.3 (1.3-4.0) | 530 |
| Nausea | | | | | | |
| All GLP-1 analogues vs comparator[11-19a] | 9 | 2.92 (2.02-4.24) | 32.9 (25.4-41.4) | 1961 | 12.6 (9.0-17.3) | 1235 |
| Exenatide vs comparator[11-17] | 7 | 3.17 (2.16-4.64) | 41.9 (36.4-47.7) | 1650 | 13.4 (9.5-18.5) | 1180 |
| Liraglutide vs placebo injection[18,19] | 2 | 0.89 (0.27-3.01) | 5.6 (3.1-10.1) | 311 | 5.7 (1.8-16.2) | 55 |
| Vomiting | | | | | | |
| All GLP-1 analogues vs comparator[11-16,18,19a] | 8 | 3.32 (2.51-4.41) | 11.6 (9.1-14.6) | 1930 | 4.0 (3.1-5.1) | 1045 |
| Exenatide vs comparator[11-16] | 6 | 3.52 (2.64-4.70) | 14.1 (12.5-15.9) | 1619 | 4.0 (3.1-5.1) | 990 |
| Liraglutide vs placebo injection[18,19] | 2 | 0.62 (0.13-2.91) | 2.3 (1.1-4.7) | 311 | 3.6 (0.9-13.4) | 55 |
| Diarrhea | | | | | | |
| All GLP-1 analogues vs comparator[11-16,18a] | 7 | 2.23 (1.72-2.89) | 10.2 (7.9-13.0) | 1751 | 4.9 (3.7-6.6) | 1136 |
| Exenatide vs comparator[11-16a] | 6 | 2.27 (1.75-2.94) | 11.0 (8.8-13.6) | 1616 | 4.9 (3.6-6.7) | 1110 |
| **DPP4 Inhibitors** | | | | | | |
| Hypoglycemia | | | | | | |
| All DPP4 inhibitors vs comparator[20-39a] | 20 | 0.97 (0.50-1.86) | 1.6 (0.7-3.2) | 4072 | 1.4 (0.6-3.4) | 3239 |
| Sitagliptin vs comparator[20-27] | 8 | 0.92 (0.30-2.87) | 1.8 (0.9-3.3) | 1978 | 1.5 (0.2-8.5) | 1673 |
| Vildagliptin vs comparator[28-39a] | 12 | 0.84 (0.60-1.19) | 1.4 (0.4-4.8) | 2094 | 1.2 (0.3-5.7) | 1566 |
| Nausea | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,29,30,33,35,38a] | 10 | 0.89 (0.58-1.36) | 2.7 (2.1-3.4) | 3591 | 3.1 (2.0-4.7) | 2034 |
| Sitagliptin vs comparator[21-25a] | 5 | 1.46 (0.88-2.43) | 2.1 (1.4-3.0) | 2126 | 1.4 (0.7-2.4) | 1362 |
| Vildagliptin vs comparator[29,30,33,35,38a] | 5 | 0.57 (0.37-0.88) | 3.4 (2.6-4.6) | 1465 | 5.2 (3.6-7.4) | 672 |
| Vomiting | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,36a] | 6 | 0.69 (0.42-1.15) | 1.3 (0.8-2.2) | 2637 | 1.5 (0.9-2.6) | 1611 |
| Sitagliptin vs comparator[21-25a] | 5 | 0.86 (0.45-1.65) | 1.1 (0.6-2.0) | 2126 | 1.2 (0.8-1.9) | 1362 |
| Vildagliptin vs comparator[38a] | 1 | 0.49 (0.21-1.11) | NR | 511 | NR | 249 |
| Diarrhea | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,35,38a] | 7 | 0.80 (0.42-1.54) | 3.8 (2.8-5.1) | 2997 | 4.0 (1.8-8.5) | 1792 |
| Sitagliptin vs comparator[21-25a] | 5 | 1.21 (0.81-1.80) | 3.6 (2.5-5.1) | 2126 | 2.8 (1.8-4.6) | 1725 |
| Vildagliptin vs comparator[35,38a] | 2 | 0.34 (0.14-0.81) | 4.0 (2.0-8.0) | 871 | 9.9 (2.7-30.7) | 611 |
| Abdominal pain | | | | | | |
| All DPP4 inhibitors vs comparator[21,23-25,38a] | 5 | 0.73 (0.36-1.45) | 2.4 (1.8-3.2) | 2149 | 3.2 (1.7-5.7) | 1468 |
| Sitagliptin vs comparator[21,23-25a] | 4 | 0.92 (0.47-1.80) | 2.5 (1.8-3.3) | 1638 | 2.6 (1.7-3.9) | 1219 |
| Vildagliptin vs comparator[38a] | 1 | 0.32 (0.16-0.66) | NR | 511 | NR | 249 |
| Cough | | | | | | |
| All DPP4 inhibitors vs comparator[21-23,25,28,29a] | 5 | 1.07 (0.65-1.78) | 2.9 (2.1-4.0) | 1639 | 2.4 (1.7-3.5) | 1238 |
| Sitagliptin vs comparator[21-23a] | 3 | 0.95 (0.54-1.66) | 2.5 (1.7-3.5) | 1363 | 2.6 (1.8-3.9) | 963 |
| Vildagliptin vs comparator[28,29a] | 2 | 1.86 (0.57-6.11) | 4.8 (2.6-8.6) | 276 | 1.7 (0.7-4.1) | 275 |
| Influenza | | | | | | |
| All DPP inhibitors vs comparator[21-24,28,29,33,35a] | 6 | 0.87 (0.64-1.19) | 4.1 (3.3-5.1) | 2118 | 4.7 (3.8-5.9) | 1727 |
| Sitagliptin vs comparator[21-24a] | 4 | 0.95 (0.65-1.39) | 4.0 (3.1-5.1) | 1538 | 4.4 (3.4-5.8) | 1141 |
| Vildagliptin vs comparator[29,35a] | 2 | 0.73 (0.42-1.27) | 4.2 (2.5-7.1) | 580 | 5.3 (3.7-7.4) | 586 |

*(continued)*

therapy (~1 and 0.7% for GLP-1 agonists and DPP4 inhibitors, respectively) is not surprising, as the physiologic role of incretins is to amplify insulin secretion. The modest effectiveness may, at least in part, be also attributed to participants' relatively low baseline $HbA_{1c}$ (~8%) compared with older trials with other currently available therapies, wherein baseline $HbA_{1c}$ was often in the 9% to 10% range. Indeed, the magnitude of the reduction in $HbA_{1c}$ with incretin therapy was dependent on the baseline $HbA_{1c}$ so that greater reductions were seen in groups of participants with higher baseline $HbA_{1c}$.[21,29,30] Incretin therapy decreased both fasting and postprandial glycemia; however, improvements in postprandial glycemic excursions were larger, based on mixed-meal tolerance testing. The preferential improvement in postprandial glycemia with incretin therapy addresses an important limitation of currently available pharmacologic therapies and provides an alternative to our limited options for targeting postprandial glycemia. In the few available trials, incretin-based medications were found to be noninferior compared with non–incretin-based pharmacologic therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide, or thiazolidinediones, with the exception of metformin being superior to vildagliptin.[38] Additional trials comparing incretin-based therapies with existing therapies are ongoing.

In contrast with nearly all available hypoglycemic agents that cause weight gain, GLP-1 analogues were associated with moderate weight loss. Weight loss was continuous, without an apparent plateau during the first 30 weeks of therapy. The weight loss may, in part, be due to nausea; however, nausea decreased over the course of the trials and participants who did not report any nausea also had weight loss. Exenatide is currently being investigated as a weight-loss medication. Dipeptidyl peptidase 4 inhibition was weight neutral overall but with an overall favorable weight profile compared with thiazolidinediones or sulfonylurea.

The low hypoglycemia event rate seen in all studies confirms the glucose-dependent action of incretins.[6] The low risk of hypoglycemia offers an advantage over other therapies, as concern for hypoglycemia is a major obstacle to medication adherence. However, hypoglycemia can still occur, especially if incretin therapy is combined with an insulin secretagogue; therefore, when

**Table 3.** Summary of Adverse Events in Patients With Type 2 Diabetes Treated With Incretin-Based vs Non–Incretin-Based Therapy (cont)

| Adverse Event | No. of Studies Contributing Data | Risk Ratio (95% CI), Incretin vs Control | Incretin-Based Therapy: Mean % (95% CI) Achieving Outcome | Incretin-Based Therapy: No. of Participants With Data Analyzed | Control: Mean % (95% CI) Achieving Outcome | Control: No. of Participants With Data Analyzed |
|---|---|---|---|---|---|---|
| **DPP4 Inhibitors** | | | | | | |
| Nasopharyngitis | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,28,29,31,34-36,38a] | 12 | 1.17 (0.98-1.40) | 6.4 (5.1-7.8) | 4201 | 6.1 (5.0-7.4) | 3321 |
| Sitagliptin vs comparator[21-25a] | 5 | 1.38 (1.06-1.81) | 5.3 (3.5-7.9) | 2126 | 4.5 (3.0-6.7) | 1362 |
| Vildagliptin vs comparator[28,29,31,34-36,38a] | 7 | 1.02 (0.80-1.29) | 7.3 (5.8-9.3) | 2075 | 7.3 (6.0-8.9) | 1057 |
| Upper respiratory tract infection | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,31,35,36,38a] | 9 | 0.99 (0.81-1.21) | 6.3 (5.1-7.7) | 3413 | 6.4 (4.9-8.4) | 2045 |
| Sitagliptin vs comparator[21-25a] | 5 | 1.09 (0.84-1.43) | 5.7 (4.0-8.0) | 2126 | 4.7 (2.8-8.0) | 1362 |
| Vildagliptin vs comparator[31,35,36,38a] | 4 | 0.88 (0.65-1.18) | 6.8 (5.3-8.6) | 1287 | 8.0 (6.5-9.8) | 683 |
| Sinusitis | | | | | | |
| All DPP4 inhibitors vs comparator[21,22,29a] | 3 | 0.61 (0.34-1.12) | 2.0 (1.3-3.1) | 1119 | 3.4 (2.4-4.8) | 419 |
| Sitagliptin vs comparator[21,22a] | 2 | 0.81 (0.41-1.58) | 2.2 (1.4-3.4) | 899 | 2.5 (1.6-3.9) | 363 |
| Vildagliptin vs comparator[29a] | 1 | 0.20 (0.05-0.78) | 1.2 (0.3-4.1) | 220 | 5.4 (3.1-9.2) | 56 |
| Urinary tract infection | | | | | | |
| All DPP4 inhibitors vs comparator[21-23,25,33a] | 5 | 1.52 (1.04-2.21) | 3.2 (2.3-4.5) | 2255 | 2.4 (1.8-3.2) | 345 |
| Sitagliptin vs comparator[21-23,25a] | 4 | 1.42 (0.95-2.11) | 3.1 (2.1-4.6) | 1951 | 2.6 (1.9-3.5) | 1184 |
| Vildagliptin vs comparator[33a] | 1 | 2.72 (0.85-8.68) | 3.6 (1.5-8.3) | 304 | 1.3 (0.5-3.3) | 158 |
| Headache | | | | | | |
| All DPP4 inhibitors vs comparator[21-25,29-31,33-36,38a] | 13 | 1.38 (1.10-1.72) | 5.1 (4.1-6.4) | 4517 | 3.9 (3.1-4.8) | 2554 |
| Sitagliptin vs comparator[21-25a] | 5 | 1.24 (0.82-1.87) | 3.6 (2.9-4.5) | 2126 | 3.1 (1.9-4.9) | 1362 |
| Vildagliptin vs comparator[29-31,33-36,38a] | 8 | 1.47 (1.12-1.94) | 6.3 (5.0-8.0) | 2391 | 4.4 (3.4-5.6) | 1192 |

Abbreviations: CI, confidence interval; DPP4, dipeptidyl peptidase 4; GLP-1, glucagonlike peptide 1; $HbA_{1c}$, hemoglobin $A_{1c}$.
[a] Comparator was placebo, oral hypoglycemic agent, or insulin.

incretin therapy is coadministered with insulin secretagogues, the dose of the latter should be adjusted to minimize hypoglycemia.

The most common adverse effects with GLP-1 analogues, seen with exenatide, were gastrointestinal (nausea and, less commonly, vomiting), which are thought to be due to inhibition of gastric emptying by GLP-1.[42,43] There appears to be development of tolerance to these adverse effects; however, nausea and vomiting were the most likely reasons for withdrawal in approximately 4% of participants. A dose escalation protocol for exenatide is recommended to minimize the gastrointestinal adverse effects.[44]

In individual studies, DPP4 inhibitors showed no characteristic pattern of adverse effects. However, our analysis showed an increased risk of infections, such as urinary tract infection and nasopharyngitis. Dipeptidyl peptidase 4 is a ubiquitous cell-membrane protein, expressed in many tissues, including lymphocytes, which has raised some concerns about the long-term effects of DPP4 inhibitors, especially on immune function.[8] Although the relative risk we measured was small, its implications in clinical practice are significant because there are more than 20 million patients with diabetes in the United States who are both more likely to develop a urinary tract infection[45] and are at higher risk of complications, including death from urosepsis.[46] A relative risk of 1.5 increases the number of urinary tract infections by 1 million new cases per year, placing a significant burden on the individual patient and the health care system. Studies of longer duration, including careful postapproval surveillance in clinical practice, are needed to assess the effects of long-term DPP4 inhibition on the immune system. Until more safety data are available, it may be prudent to avoid use of these agents in patients with a history of recurrent urinary tract infections.

There was also a slight increase in the relative risk of headache with DPP4 inhibitors, which does not appear to be related to hypoglycemia. Until the risk is further defined, it may be prudent to avoid use of DPP4 inhibitors in patients with a history of chronic headache.

Nearly all trials lasted less than 30 weeks, limiting our assessment of long-term efficacy and safety. Long-term data are particularly important for the newest class, the DPP4 inhibitors, especially given our finding of increased risk of infection. Most studies included predominantly white participants; therefore, differential effects of incretin-based therapy by race or ethnicity could not be assessed. Our results also do not apply to children since none were studied. Finally, most studies did not use a true intention-to-treat analysis, defined as all randomized patients, which may have overestimated the glycemic efficacy especially given the relatively high dropout rate (~20% of participants).

Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant adults with type 2 diabetes with modest efficacy and a favorable weight change profile. Although in individual short-term studies, the DPP4 inhibitors appear safe, our meta-analysis showed an increased risk of certain infections and headache. Individuals with mild diabetes, suggesting an adequate pancreatic β cell reserve, who are at risk of hypoglycemic sequelae and in need of weight loss may benefit from this new class. However, these new classes of hypoglycemic agents will need continued evaluation both in long-term efficacy and safety controlled trials and in clinical practice to assess their effectiveness and safety profile to determine their role among the many available and well-established therapies for type 2 diabetes.

**Author Contributions:** Drs Amori and Pittas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Amori, Pittas.
*Acquisition of data:* Amori, Pittas.
*Analysis and interpretation of data:* Amori, Lau, Pittas.
*Drafting of the manuscript:* Amori, Pittas.
*Critical revision of the manuscript for important intellectual content:* Amori, Lau, Pittas.
*Statistical analysis:* Lau, Pittas.
*Obtained funding:* Pittas.
*Administrative, technical or material support:* Amori.
*Study supervision:* Lau, Pittas.
**Financial Disclosures:** None reported.

**Funding/Support:** This work was supported by grant K23 DK61506 (to Dr Pittas) from the National Institute of Diabetes and Digestive and Kidney Diseases and by a grant to the Dr Gerald J. and Dorothy R. Friedman New York Foundation for Medical Research (to Dr Amori).
**Role of the Sponsor:** The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretations of the data; or preparation, review, or approval of the manuscript.
**Additional Contribution:** We thank Thomas Trikalinos, MD, Institute for Clinical Research and Health Policy Studies, Tufts-New England Medical Center, Boston, Massachusetts, for help with the statistical analyses. Dr Trikalinos did not receive compensation for his work.

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